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by

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16. ABSTRACT

The evaluation of emissions from new energy sources has stimulated the development of new comparative approaches to health assessment studies. All energy sources that result in incomplete combustion are known to emit carcinogenic and mutagenic polynuclear aromatic compounds. Therefore, any toxicological assessment requires a comparative analysis of the new technology compared to the conventional technology. We have evaluated the mutagenicity and carcinogenicity of emissions from various conventional and alternative combustion sources and fuels in comparative studies utilizing a battery of short-term genetic bioassays in conjunction with animal cancer studies. The mutagenicity and carcinogenicity of these emissions have also been compared to several complex emission products for which human lung cancer risks have been estimated. This approach has allowed the estimation of human lung cancer risks from future energy sources using short-term genetic bioassay data. The combustion sources examined include heavy-duty and light-duty diesel and gasoline fueled vehicles, residential oil and wood heaters, and both small and large utility power plants. The comparative approach to evaluating the emissions from the combustion of alternative fuels, such as synfuels, involves parallel bioassay studies of these emissions with emissions from conventional fuels.

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COMPARATIVE APPROACH TO EVALUATING RELATIVE CANCER RISKS FROM ENERGY SOURCES USING SHORT-TERM GENETIC BIOASSAYS

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INTRODUCTION

Short-term genetic bioassays are now widely employed to screen both individual chemicals (e.g., pesticides and toxic substances) and complex mixtures (e.g., industrial effluents, automotive emissions) for mutagenic and potential carcinogenic activity. These bioassays are often employed in a tiered or phased approach to prioritize substances for more expensive chronic animal testing[1,2]. The results of both microbial and mammalian cell genetic bioassays are now considered by governmental regulatory agencies and international organizations to provide important suggestive evidence of a substance's carcinogenicity in humans[3,4].

The assessment of potential human risk from the introduction of new alternative energy sources and synthetic fuels presents a somewhat different problem than introducing a new chemical into commerce. That problem results from the fact that the combustion emissions from the conventional energy sources and fuels currently in use contain carcinogenic polycyclic organic compounds which are mutagenic in short-term microbial and mammalian cells[5-7] and are tumorigenic in animals[8]. The greatest concern regarding the introduction of new energy sources, including synthetic fuels, is whether they will increase the mutagenicity, carcinogenicity, and potential human cancer risk from combustion emissions. The widest human exposures to synthetic fuels is from the end use of these products as energy sources in combustion technologies for heating, power generation, or transportation[9]. Relatively rapid and inexpensive toxicological methods are needed to assess synthetic fuels as they are being developed so that alternative methods of extraction, production, and refining can be evaluated with respect to the alternative hazard of combustion emissions from the end product.

In order to assess the relative human cancer risk associated with introducing diesel-powered automobiles as an alternative fuel-efficient energy source for transportation, we have developed a comparative data base[10,11] and risk assessment methodology[12]. Although this method was initially developed

to compare alternative combustion sources (e.g., engines) which are powered by different fuels (e.g., diesel vs. gasoline), this risk assessment model and methodology is applicable to the evaluation of various fuels. This paper describes a comparative approach to evaluating alternative energy sources, including synthetic fuels, by utilizing short-term genetic bioassays.

COMPARATIVE POTENCY METHOD

The comparative potency method for cancer risk assessment is based on the hypothesis that there is a constant relative potency between two different carcinogens across different bioassay systems. This assumption is implicit in any comparison which utilizes the relative toxicity of two substances in animals to determine which substance would most likely be less toxic to man. This constant relative potency assumption is a testable hypothesis, if the relative potency of two carcinogens in humans can be determined and compared to the relative potency in a series of in vitro and in vivo bioassays.

We have tested this hypothesis for three complex organic emissions from a coke oven, roofing tar pot, and cigarettes by using human lung cancer data from epidemiological studies of humans exposed to these emissions[12]. The relative potencies for coke oven compared to roofing tar were similar and ranged from 0.2-1.4 across data from humans, mouse skin tumor imitiation, and selected short-term genetic bioassays as shown in Table 1. When the relative potency for cigarette smoke was compared to roofing tar or coke ovens, however, the short-term bioassays showed a much higher relative potency than the human and mouse skin tumor initiation bioassay. A series of diesel and gasoline automotive emissions, for which no human data were available, were also tested in the battery of in vivo and in vitro bioassays. The relative potency within the automotive samples across these bioassays was, however, relatively constant as shown in Table 2. High correlations were observed between the mutagenic activity of these emissions and their tumor initiating activity[6].

This method was initially applied to the estimation of a human life-time cancer risk (unit risk) for a series of diesel automobiles by comparison to the human cancer unit risk from coke oven, roofing tar, and cigarette according to the following equation (e.g., for coke oven emissions):

human risk (diesel/coke oven) = relative bioassay potency (diesel/coke oven)

The relative potency in the mouse skin tumor initiation bioassay was used to estimate the unit risk of one diesel emission. The average relative potencies in the short-term genetic bioassays were used to estimate the unit risks for the other diesel and gasoline samples. This approach to applying the comparative

TABLE 1

COMPARISON OF RELATIVE POTENCIES OF EMISSION EXTRACTS IN HUMANS AND BIOASSAY SYSTEMS[a]

Emission Extracts	Human Lung Cancer	Mouse Skin Tumor Initiation	Mutation in Mouse Lymphoma Cells (+MA)	Mutation in Ames TA98 (+MA)
Coke Oven	1.0	1.0	1.0	1.0
Roofing Tar	0.39	0.20	1.4	0.78
Cigarette	0.0024	0.0011	0.066	0.52
Diesel (Nissan)		0.28	0.24	12.

[a]The relative bioassay potencies were determined for each of the bioassay systems by dividing the absolute activity (e.g., lung cancer risk, tumor initiation activity or mutagenicity) of each emission by the activity of the coke oven emission within that bioassay[12]. The mouse skin tumor initiation data[8,19], mouse lymphoma data[18], and Ames data[13] are reported and evaluated elsewhere[6,12]. The collection and preparation of emission extracts have been previously reported[10].

TABLE 2

COMPARISON OF RELATIVE POTENCIES OF DIESEL AND GASOLINE EMISSION EXTRACTS IN SEVERAL BIOASSAY SYSTEMS[a]

Emission Extracts	Mouse Skin Tumor Initiation	Mutation in Mouse Lymphoma Cells (-MA)	Mutation in Mouse Lymphoma Cells (+MA)	SCE in CHO Cells (-MA)	SCE in CHO Cells (+MA)	Mutation in Ames TA98 (-MA)	Mutation in Ames TA98 (+MA)
DIESELS							
Nissan	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Volkswagen Rabbit	0.41	0.23	0.25	0.25	0.42	0.34	0.23
Oldsmobile	0.53	0.29	0.45	Neg	0.24	0.19	0.11
Caterpillar	Neg	0.06	0.022	0.037	Neg	0.034	0.023
GASOLINE CATALYST							
Mustang II	0.29	0.90	0.38	0.25	NT	0.26	0.26

[a]The relative potencies were determined by dividing the tumorigenicity or mutagenicity (linear slope of the dose-response) of each emission by the activity of the Nissan diesel within that bioassay. Several emissions were either negative (Neg) or not tested (NT) due to insufficient amounts of sample. The data for each assay are reported elsewhere[6,8,12,13,18,19]. The generation, collection, and preparation of these automotive emissions have been previously reported[6,10].

potency method assumes that when comparing between one of the three human carcinogens and the automotive emissions, the mouse skin best predicts the relative potency compared to humans. Within the automotive emissions, however, it was assumed that an average relative potency in short-term bioassays can be used to estimate the human risk since the relative potencies in the short-term bioassays correlated so well with the mouse skin tumor-initiating activity[12].

The major assumption and main source of uncertainty in this comparative potency method is the validity of the constant relative potency hypothesis. Interspecies differences in absorption and metabolism, which present the most difficult problems in extrapolation from animals to humans, may also effect the relative carcinogenic potency. By developing and evaluating a comparative data base across human, animal, and short-term bioassays for the same substances, these assumptions can be tested. The constant relative potency model does not assume "a priori" that the carcinogens being compared are chemically similar. The coke oven, roofing tar, cigarette smoke, and automotive emission samples are similar in that they all contain polycyclic organic compounds which cause frameshift mutations in Salmonella typhimurium[5]. These four emissions differed in their metabolic activation requirements[13], and upon chemical fractionation and characterization significant differences were observed in the specific mutagenic/carcinogenic chemicals present[14]. The similarity in chemical composition of the different diesel automobile emissions may be the basis for the constant relative potency observed across the short-term bioassays and animal tumorigenicity for this series of emissions. The mutagens and carcinogens present in these mixtures may differ only in their concentration.

This comparative potency method provides a framework for evaluating alternative energy sources and fuels by comparing them to the conventional technologies in short-term genetic bioassays. It is possible to extend the method described here for estimating lung cancer unit risks for diesel and gasoline automotive emissions to unit risk estimates for various synfuels through the data base established linking human, animal, and short-term genetic bioassay data. A simplified comparative approach to evaluating alternative energy sources is to employ parallel bioassay studies of the alternative (a) and conventional (c) source emissions and determine a relative risk by direct comparison as follows: increased risk (a/c) = relative bioassay potency (a/c). Since there is no one conventional standard petroleum-derived fuel or one standard combustion source, such studies need to consider the range of mutagenic and carcinogenic potency between different conventional sources and fuels. The establishment of such a range could then serve as a guide for evaluating

alternative fuels. For example, if the relative potency of the alternative fuel emissions fell within the range for the conventional fuels, one could assume no increased human risk. The battery of bioassays to be employed in such a study would depend upon availability of emission sample, resources, and time. As more bioassays are employed, however, confidence in the relative potency estimates should increase.

TABLE 3

RANGE OF MUTAGENIC EMISSION RATES FROM NO. 2 DIESEL PETROLEUM FUELS[a]

Diesel Vehicle	MA	Mutagenic Activity/km: Mutation in Ames TA98 ($x10^5$) Range	Mutation in Mouse Lymphoma Cells ($x10^5$) Range	SCE in CHO Cells ($x10^4$) Range
Truck (Ford/Cat)	-	6.8-14. (2.1x)	0.91-3.5 (3.8x)	0.21-6.6 (31x)
	+	5.2-17. (3.3x)	0.85-1.4 (1.6x)	1.2 -2.1 (1.7x)
Bus (GM/Detroit)	-	0.22-1.1 (5.0x)	----	0.91-2.8 (3.1x)
	+	0.37- .86 (2.3x)	1.3-4.3 (3.3x)	0.72-1.7 (2.4x)

[a]The mutagenic emission rate, mutagenic activity/km, was determined from the mutagenic activity dose-response slope of the particulate emission extracts, the percent organic extractables and particulate emission rates for each vehicle. The mutagenic emission rate units for each bioassay are as follows: Ames (revertants/km $x10^5$), mouse lymphoma (mutants/10^6 survivors/μg/ml/km $x10^5$), SCE in CHO cells (SCE/cell/μg/ml/km $x10^4$). The range in activity between the different fuels is shown in parentheses e.g., (2.1x) for each bioassay. The truck (Ford/Cat) was a heavy-duty Bob Tail Van (LN-7000) with a Caterpillar 3208 engine. The bus (GM/Detroit) was a General Motors city bus with a Detroit diesel DD8V-71 engine. Both vehicles were operated on the 83 transient cycle with premium (EM-242F), average (EM-239F) and minimum quality (EM-241F) petroleum derived diesel fuels. The specifications and chemical composition of these fuels have been previously reported[22].

The range of mutagenic activity (e.g., rev/μg) and mutagenic emission rate (e.g., rev/km) in a battery of short-term genetic bioassays has been compared between a series of petroleum-derived fuels which meet the specifications for No. 2 diesel fuel for automobiles. Within these specifications, however, is a range of fuels from minimum quality fuels (high nitrogen, sulfur and aromatic content and low cetane value) to premium quality fuels (low sulfur, nitrogen, and aromatic content and high cetane value). Table 3 shows the range in mutagenic emission rates for three short-term bioassays when three No. 2 diesel fuels were combusted in two vehicles. The mutagenic emission rates generally ranged from 2-5 fold except for the SCE assay for the truck emissions in the absence of S9 which showed a 31-fold range.

The combustion emissions from synfuels with chemical compositions significantly different from petroleum-derived fuels could be evaluated in the same bioassays to determine if the relative risk from these emissions is increased by a factor significantly greater than the differences observed between currently utilized petroleum-derived fuels.

EXPERIMENTAL METHODS

Emission sample collection and extraction methods. Combustion emissions containing both gaseous and particulate matter are typically collected by filtration or electrostatic precipitation after dilution and cooling[15,16] or are directly collected by condensation[17]. The automotive emissions described here as well as the residential oil and wood combustion emissions were collected by a modification of the standard dilution tunnel method[10,15] where the exhaust is collected on large 20"x20" Teflon-coated Pallflex T60-A20 filters. The collection methods for the coke oven, roofing tar, and cigarette smoke condensate have been described elsewhere[10]. The particulate samples were Soxhlet extracted with dichloromethane (DCM) for 48 hr, filtered (0.2 μm pore) and the DCM removed by evaporation and solvent-exchanged into dimethylsulfoxide (DMSO) for all the bioassays discussed here except for mouse skin tumorigenesis where acetone was used as the solvent.

Bioassay methods. The short-term genetic bioassays in which dose-dependent and reproducible increases in response were obtained for many of the combustion emission samples evaluated included:

1. Reverse mutation in Salmonella typhimurium TA98 (Ames bioassay)[13]
2. Forward mutation at the thymidine kinase locus in L5178Y mouse lymphoma cells (mouse lymphoma bioassay)[18]
3. Sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells (SCE bioassay)[18]

For these bioassays, one or more preliminary range-finding tests were performed to determine the optimum dose range for defining the slope of the dose-response. The bioassays were generally performed with duplicate or triplicate treatments at five to seven doses. The bioassays were all performed in the presence and absence of an Aroclor-induced rat liver S9 metabolic activation system (MA). The linear slope of the dose-response determined from simple regression analysis was utilized for the comparative potency analysis as previously described[12].

Mouse skin tumorigenesis assays which have had considerable use in determining the tumorigenic and carcinogenic effects of chemicals and complex mixtures,

were performed in SENCAR mice as previously described[8] utilizing five single doses (80 mice/dose) and scoring individually at six months for papillomas and at one year for squamous cell carcinomas[19]. The carcinoma responses in the initiation assay were correlated with the papilloma responses; only the papilloma responses were used in the comparative potency analysis[12].

COMPARATIVE ASSESSMENT OF ALTERNATIVE ENERGY SOURCES

Short-term bioassays have proven useful in evaluating the effects of various engines, fuels, and control technologies on the mutagenicity of emissions. To draw meaningful conclusions from such comparisons, however, the normal day-to-day variations in the emissions were studied for one engine under standard conditions[20]. The coefficients of variation (CV) for the particulate emission rates, percent organic extractables, and mutagenic activity ranged from 0.07 to 0.11. To compare the mutagenicity of particulate emissions from different sources or fuels, the percent of organic material extractable from the particles and the vehicle's particulate emission rate must also be included in the analysis. The final rate of mutagenic emissions is determined from all three parameters.

Although pure compounds have been reported to range in carcinogenic and mutagenic potency over six orders of magnitude[21], the relative potency of combustion emissions ranged from only a five-fold difference in the mouse skin tumorigenesis assay to a 150-fold difference in the mouse lymphoma gene mutation assay. The Ames Salmonella typhimurium mutagenesis assay showed approximately two orders of magnitude difference (100-110 fold) in mutagenic activity (rev/μg) from the weakest to the most potent emission sample. The emission rates (rev/km or rev/J) for the particle-bound organics, however, differed in some cases by as much as five orders of magnitude (10^5). To compare the mutagenicity of emissions from various sources, it is critical to compare the rates of mutagenic emissions on the same basis (e.g., fuel consumption, distance driven, energy consumption, or yield). To compare rates of mutagenic emissions of mobile sources, we have compared the mutagenic activity per kilometer, as shown in Table 4. The rates of mutagenic emissions from stationary sources are compared on the basis of fuel or energy consumption, as shown in Table 5.

This direct comparative analysis of mutagenic emission rates provides a simple means of evaluating alternative energy sources. It is apparent from this data base that the organic emission rate may vary more than the mutagenicity or carcinogenicity of the emissions; and, therefore, in the final analysis has a greater impact on the relative carcinogenic risk from those sources.

TABLE 4

COMPARATIVE MUTAGENIC EMISSION RATES FOR TRANSPORTATION COMBUSTION SOURCES[a]

Vehicles	Fuel type	Mutagenicity of Organics: Ames TA98 (+MA)	Mutagenicity of Organics: Mouse Lymphoma (+MA)	Organic Emission Rate (mg/km)	Mutagenic Emission Rates (activity/km): Ames TA98 ($\times 10^5$)	Mutagenic Emission Rates (activity/km): Mouse Lymphoma ($\times 10^5$)
Diesel engine						
Car (Mercedes)	diesel	12.0	1.5	19.2	2.4	0.30
Truck (Ford/Cat)	diesel	1.7	0.28	302.0	5.3	0.85
Bus (GM)	diesel	0.1	0.35	357.0	.37	1.3
Gasoline engine						
Non-catalyst (Ford Van)	unleaded gasoline	32.0	5.7	5.7	1.8	0.32
Catalyst (Mustang II)	leaded gasoline	3.5	1.1	1.4	.05	0.02

[a]The mutagenicity of the organics in the Ames bioassay is expressed in revertants/μg (rev/μg) and in the mouse lymphoma bioassay as mutants/10^6 survivor/μg/-ml (mut. freq./μg/ml). The mutagenic emission rates were determined as described in Table 3. The methods for collecting these emissions and performing the mutagenesis bioassays have been reported elsewhere[6,10,14].

TABLE 5

COMPARATIVE MUTAGENIC EMISSION RATES FOR STATIONARY COMBUSTION SOURCES[a]

Residential	Fuel type	Mutagenicity of Organics Ames TA98 (rev/μg)	Organic Emission Rate (ng/J)	Mutagenic Emission Rate (rev/J) ($\times 10^3$)
Woodstove (airtight)	Pine	1.3	508.0	660.0
Woodstove (airtight)	Oak	0.9	187.0	168.0
Oil furnace #1	Oil #2	2.0	0.5	1.0
Oil furnace #2	Oil #2	5.1	1.5	7.6
Utility power plants				
Conventional	coal	3.1	0.01	0.031
Fluidized-bed	coal	9.4	0.03	0.28

[a]The mutagenic emission rates were determined as described in Table 3. The mutagenicity of these stationary source combustion emissions have been reviewed elsewhere[14]. The mutagenicity of the woodstove and oil furnace emissions is shown in the presence of metabolic activation (MA) and the utility coal power plant emissions in the absence of MA.

COMPARATIVE EVALUATION OF ALTERNATIVE FUELS

Fuel composition may effect the mutagenic and potential carcinogenic activity of combustion emissions by (1) direct contribution of mutagens in the fuel, (2) by contribution of compounds which when combusted give rise to mutagens, or (3) by influencing the combustion process so that generation of mutagenic and carcinogenic compounds are altered. The influence of fuel composition on the mutagenicity of diesel emissions was initially examined for five petroleum derived fuels, in two light-duty diesel vehicles[22]. In one vehicle, the emissions from the minimum-quality fuel, with a higher aromatic and nitrogen content, were approximately 5 times more mutagenic per milligram particulate emission in the Ames mutagenesis bioassay than were the emissions from the other fuels. The emissions from these fuels did not differ significantly in mutagenicity, however, when they were burned in the second vehicle. Similar mutagenesis studies were conducted when the same fuels were combusted in the three heavy-duty vehicles[23]. The minimum-quality fuel produced a higher rate of mutagenic emissions in two of the vehicles; however, this difference was not observed for the third vehicle.

Since aromaticity and nitrogen content were implicated as influencing the microbial mutagenicity of diesel emissions, a study was designed to examine these two parameters by the use of aromatic and nitrogen additives to a base fuel[24]. Nonmutagenic nitrogen fuel additives, hexylnitrate and isoquinoline, had little effect on the mutagenicity of the diesel emissions. In this study the emissions from the three fuels with higher aromatic content of 30-35% compared to fuels with 3-7% aromatics were more mutagenic; however, the differences were small and within the ranges shown in Table 3 above. A second study designed to examine correlations between nitrogen content, aromatic content, and the concentrations of specific polycyclic aromatic hydrocarbon content (e.g., fluoranthene, pyrene, and benzo[a]pyrene) in six different petroleum fuels in one diesel engine and five petroleum fuels in a second engine found the highest correlations between mutagenicity and nitrogen content[25].

These studies suggest that although poorer-quality fuel, with relatively high aromatic and nitrogen content, can result in increased rates of mutagenic emissions in certain vehicles, such differences are not observed in all vehicles. In general, the observed changes in mutagenic activity of emissions as a function of fuel quality were much smaller than the differences between different types of engines (e.g., diesel vs. gasoline) and control technologies (catalyst-equipped vs. non-catalyst-equipped vehicles).

The lack of availability of synfuels for combustion testing programs currently limits the availability of bioassay data. A refined and hydrotreated shale-

derived No. 2 diesel fuel which has a higher purity with respect to nitrogen and aromatic content than comparable petroleum derived fuels is the only synfuel that has been available for a comparative combustion testing program in mobile sources[26]. Table 6 summarizes results from several studies with this fuel compared to either the national average fuel[26] or a range of No. 2 diesel fuels from minimum through premium quality. This highly refined shale fuel did result in higher mutagenic emission rates, outside the range of petroleum fuels, for one vehicle; however, this was not the case for the other two vehicles. Further combustion studies are needed to evaluate the emissions from synfuels which may differ more significantly from the petroleum fuels.

TABLE 6

MUTAGENIC EMISSION RATES FROM SHALE DERIVED SYNFUEL COMPARED TO PETROLEUM FUELS[a]

		Mutagenic Activity/km in Ames TA98 ($x10^5$)	
Diesel Autos	MA	Petroleum Fuels	Shale Derived Fuel
VW Rabbit 1	-	1.9-2.3	5.1
	+	2.2-2.7	3.5
Oldsmobile	-	1.2-2.4	1.8
	+	0.92-1.6	0.55
VW Rabbit 2	-	1.01	1.73
	+	0.76	1.09

[a]The mutagenic emission rates were determined as described in Table 3. The petroleum No. 2 fuels included a premium, average, and minimum quality fuel as described in Table 3 except for the VW Rabbit 2 study which employed a National average fuel for comparison. The shale and National average fuels and methods utilized to generate, collect the samples, and perform the bioassay have been previously described[26].

The increased or decreased human cancer risk from combustion emissions may be of greater concern than the absolute risk from these emissions when we consider the effect of alternative energy technologies and alternative synthetic fuels. The data of greatest value in determining this increased or decreased risk is comparative bioassay data on emissions from the synfuel being evaluated and its petroleum analog(s) or comparative bioassay data on the conventional and alternative technology being evaluated. The U.S. Environmental Protection Agency has developed a comparative synfuels testing program which will utilize two stationary sources (a package boiler and a diesel) to evaluate a wide range of synthetic fuels including coal and shale-derived fuels and their petroleum

analog(s)[27]. Results from such studies could be utilized in a direct comparative potency assessment of the increased or decreased cancer risk from the combustion of these fuels. Such studies should be useful in directing the way for engineers and chemists to design alternative energy sources and synfuels which result in less mutagenic and potentially carcinogenic emissions.

DISCLAIMER

This paper has been reviewed by the Office of Research and Development, U.S. Environmental Protection Agency and has been approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the U.S. Environmental Protection Agency.

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